(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 103 357**
**A2**

# (12) EUROPEAN PATENT APPLICATION

(21) Application number: 83303506.6

(22) Date of filing: 17.06.83

(51) Int. Cl.³: C 07 D 233/72, C 07 D 295/12

(30) Priority: 22.06.82 US 391198

(43) Date of publication of application: 21.03.84 Bulletin 84/12

(84) Designated Contracting States: AT BE CH DE FR GB IT LI LU NL SE

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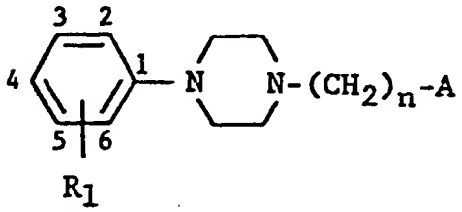
## (54) Substituted phenylpiperazine compounds suitable as antihypertensive agents, and processes for their production.

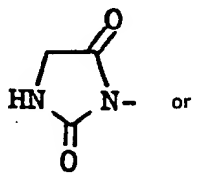
(57) Certain substituted phenylpiperazine compounds suitable for use an antihypertensive agents are described, as are processes for their preparation.

The novel compounds have the formula:



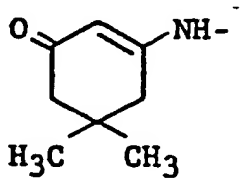
I

wherein A is



$A_1$

or



$A_2$

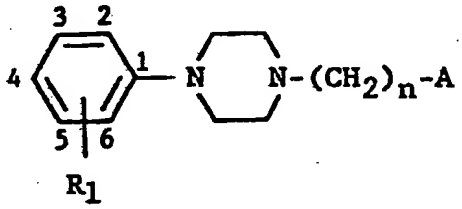
n is 2, 3 or 4; and $R_1$ is a hydrogen atom, an alkyl radical having from one to six carbon atoms or an alkoxy radical having from one to six carbon atoms; or a pharmaceutically acceptable salt thereof; with the provisos that: when A is $A_1$ and n is 3, $R_1$ is not 3-$OCH_3$; when A is $A_2$ and n is 3, $R_1$ is not 2-$OCH_3$ or 4-$OCH_3$; and, when A is $A_2$ and n is 4, $R_1$ is not 4-$CH_3$ or 4-$OCH_3$.

EP 0 103 357 A2

# SUBSTITUTED PHENYLPIPERAZINE COMPOUNDS SUITABLE AS ANTIHYPERTENSIVE AGENTS, AND PROCESSES FOR THEER PRODUCTION

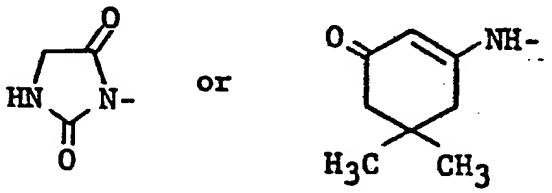
This invention relates to novel substituted phenylpiperazine compounds which are useful pharmaceutical agents for the treatment of hypertension; to processes for producing the compounds; and to pharmaceutical compositions incorporating such compounds.

In accordance with one aspect of the present invention, there is provided a compound having the structural formula I



I

wherein A is



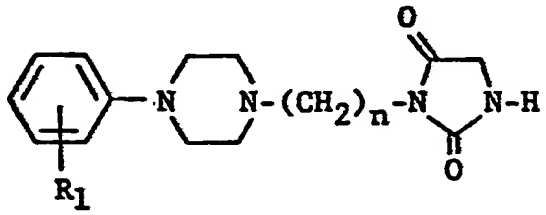
$A_1$ $A_2$

n is 2, 3 or 4; $R_1$ is a hydrogen atom, an alkyl radical of from one to six carbon atoms or an alkoxy radical of from one to six carbon atoms; or a pharmaceutically acceptable salt

thereof; with the provisos that: when A is $A_1$ and n is 3, $R_1$ is not 3-$OCH_3$; when A is $A_2$ and n is 3, $R_1$ is not 2-$OCH_3$ or 4-$OCH_3$; and, when A is $A_2$ and n is 4, $R_1$ is not 4-$CH_3$ or 4-$OCH_3$.

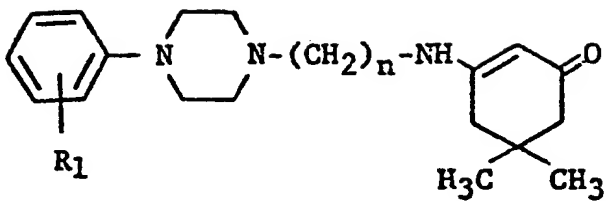
The aforementioned provisos are all necessary in order to exclude inactive compounds, with the exception of the proviso where A is $A_2$ and $R_1$ is 2-$OCH_3$. This exception is necessitated by German Offenlegungshrift 2638184 which describes the excluded compound as an intermediate in the production of the N-oxide, the latter being the compound claimed in that Offenlegungshrift as having hypotensive properties.

In accordance with a first particular aspect of the present invention, there is provided a compound having the structural formula



wherein n is 2, 3 or 4; $R_1$ is a hydrogen atom, an alkyl radical having from one to six carbon atoms, or an alkoxy radical having from one to six carbon atoms; or a pharmaceutically acceptable salt thereof; provided that, when n is 3, $R_1$ is not 3-$OCH_3$.

In accordance with a second particular aspect of the present invention, there is provided a compound having the structural formula



wherein n is 2, 3 or 4; $R_1$ is a hydrogen atom, an alkyl radical having from one to six carbon atoms, or an alkoxy radical having from one to six carbon atoms; or a pharmaceutically acceptable salt thereof; provided that, when n is 3, $R_1$ is not 2-$OCH_3$ or 4-$OCH_3$, and, when n is 4, $R_1$ is not 4-$CH_3$ or 4-$OCH_3$.

In accordance with a third particular aspect of the present invention, there is provided a compound having the structural formula I wherein $R_1$ is located at either the 3- or 4-position of the benzene ring; or a pharmaceutically acceptable salt thereof; with the provisos that: when A is $A_1$ and n is 3, $R_1$ is not 3-$OCH_3$; when A is $A_2$ and n is 3, $R_1$ is not 4-$OCH_3$; and, when n is 4, $R_1$ is not 4-$CH_3$ or 4-$OCH_3$.

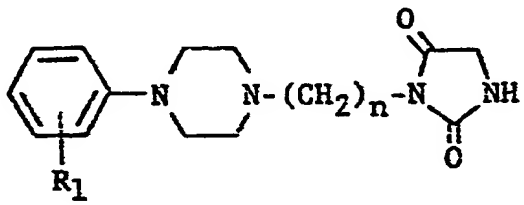
There are provided, in accordance with three specific embodiments of the present invention, the compounds having the names: 3-[4-[4-(3-methylphenyl)-1-piperazinyl]butyl] hydantoin; 3-[4-[4-(4-methylphenyl)-1-piperazinyl] butyl]hydantoin; and 5,5-dimethyl[3-[[4-(3-ethoxyphenyl)-1-piperazinyl]butyl]amino]-cyclohex-2-en-1-one; and the pharmaceutically acceptable salts thereof.

Pharmaceutical compositions of the present invention, suitable for use in treating hypertension in a mammal, comprise a compound having the structural formula I or a pharmaceutically

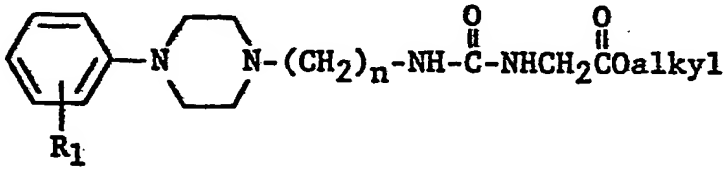
acceptable salt, or mixtures thereof, in combination with a pharmaceutically acceptable carrier.

The compounds of the present invention may be readily produced by the following processes.

The compounds of the present invention having the structural formula I wherein A is $A_1$, i.e.



, may be prepared by heating a correspondingly substituted, disubstituted urea compound of the following formula II

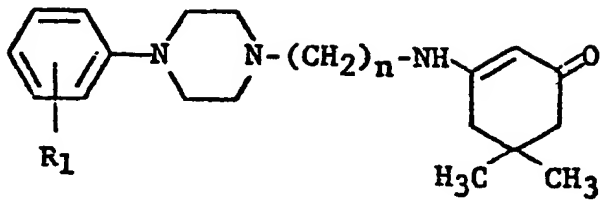


II

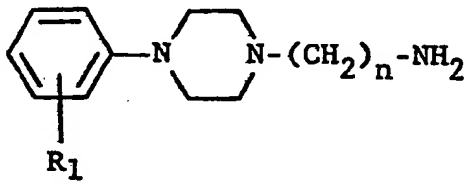
where $R_1$ and n are as defined above, or a salt thereof, in the presence of a strongly acidic or basic ring closure agent. This ring closure may be performed by a well known procedure, for example as described in U.S. Patent 3,806,510. In the above formula II, the term "alkyl" is defined as any convenient alkyl group, preferably of from one to six carbon atoms and most preferably methyl or ethyl.

The compounds of the invention having

structural formula I wherein A is $A_2$, i.e.



, may be prepared by condensing a correspondingly substituted 4-($R_1$-substitutedphenyl)-1-piperazinyl-alkylamine having the structural formula III



III

with 5,5-dimethyl-1,3-cyclohexanedione, which compound is known as dimedone. This condensation may be performed by a well known procedure, for example as described in U.S. Patent 3,879,395. In the above formula III $R_1$ and n are as previously defined.

The above described starting materials of formulae II and III may be readily prepared by procedures known in the art, as for example in U.S. Patents Nos. 3,879,395; 3,806,510; and 2,836,595.

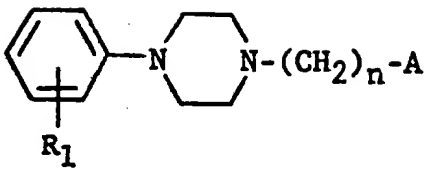
In the process for producing a compound of formula I where A is $A_1$ or $A_2$, the compound of formula I can, after its formation, be isolated and, if desired, converted into the

appropriate pharmaceutically acceptable salt.

The compounds of the present invention are new chemical substances which are useful pharmaceutical agents for the treatment of hypertension. The antihypertensive effect of representative compounds of the present invention was established by the following standard procedure.

Spontaneously hypertensive male rates (Charles River, Wilmington) weighing between 325-395 grams were cannulated for directly monitoring arterial blood pressure and heart rates. Three or four rats were orally dosed with each test compound dissolved/suspended in 4% gum acacia. The rats received 10 mg/kg body weight of test compound and were continuously monitored for blood pressure and heart rate changes for up to 24 hours postdrug. If blood pressure fell in at least two of the rats tested by at least 10% for at least two consecutive hours (4-30 minute periods), that compound was considered "active" in this test.

Representative compounds of the invention gave the following results when tested by the above-identified procedure.



| $R_1$ | n | A | % Δ bp at one hour |
|---|---|---|---|
| H | 3 | $A_1$ | -22 |
| 2-$CH_3$ | 4 | $A_1$ | -41 |
| 3-$CH_3$ | 4 | $A_1$ | -48 |
| 4-$CH_3$ | 4 | $A_1$ | -34 |
| 2-$OCH_3$ | 2 | $A_1$ | -33 |
| 2-$OCH_3$ | 3 | $A_1$ | -37 |
| 2-$OCH_3$ | 4 | $A_1$ | -19 |
| 3-$OC_2H_5$ | 4 | $A_1$ | -18 |
| H | 3 | $A_2$ | -29 |
| 2-$CH_3$ | 4 | $A_2$ | -19 |
| 3-$CH_3$ | 3 | $A_2$ | -12 |
| 3-$CH_3$ | 4 | $A_2$ | -27 |
| 2-$OCH_3$ | 4 | $A_2$ | -41 |
| 3-$OCH_3$ | 3 | $A_2$ | -15 |
| 3-$OC_2H_5$ | 4 | $A_2$ | -27 |

The compounds of the invention form pharmaceutically acceptable salts with organic and inorganic acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic, and the like. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid in the conventional manner. The free base forms may be regenerated by treating the salt form with a base. For example, dilute aqueous base solutions may be utilized. Dilute aqueous sodium hydroxide, potassium carbonate, ammonia, and sodium bicarbonate solutions are suitable for this purpose. The free base forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but the salts are otherwise equivalent to their respective free base forms for purposes of the invention.

The compounds of the invention can exist in unsolvated as well as solvated forms, including hydrated forms. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol, and the like are equivalent to the unsolvated forms for purposes of the invention.

The alkyl and alkoxy groups contemplated by the invention comprise both straight and branched carbon chains of from one to about six carbon atoms. Representative of such groups are methyl, ethyl, isopropyl, pentyl, 3-methylpentyl, methoxy, ethoxy, 2-propoxy, 3-methylpentoxy, and the like. Preferred are methyl, ethyl, methoxy, and ethoxy.

The compounds of the invention comprise an unbranched alkylene chain $-(CH_2)_n-$ wherein n is the integer 2, 3, or 4. Preferably, n is the integer 3 or 4.

The compounds of the invention comprise an $R_1$-substitutedphenyl group which substituent, $R_1$, may be located at either the 2-, 3-, or 4-position of the benzene ring. Preferably, $R_1$ is located at the 3- or 4-position of the benzene ring.

The compounds of the invention can be prepared and administered in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise as the active component, either a compound of formula I, or a corresponding pharmaceutically acceptable salt of a compound of formula I, or a mixture of such compounds and/or salts.

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersable granules, capsules, cachets, and suppositories. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active compound. In the tablet the active compound is mixed with carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from 5 or 10 to about 70 percent of the active ingredient. Suitable solid carriers are magnesium carbonate, magnesium sterate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as

carrier providing a capsule in which the active component (with or without other carriers) is surrounded by carrier, which is thus in association with it. Similarly, cachets are included. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

Liquid form preparations include solutions suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection. Liquid preparations can also be formulated in solution in aqueous polyethylene glycol solution. Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing, and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, i.e., natural or synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other well-known suspending agents.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, for example, packeted tablets, capsules and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet, or tablet itself or it can be the appropriate number of any of these packaged forms.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from 1 mg to 100 mg according to the particular application and the potency of the active ingredient.

In therapeutic use as antihypertensive agents, the compounds utilized in the pharmaceutical method of

this invention are administered at the initial dosage of about 1 mg to about 30 mg per kilogram daily. A daily dose range of about 3 mg to about 10 mg per kilogram is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The following nonlimiting examples illustrate the inventor's preferred methods for preparing the compounds of the invention.

EXAMPLE 1

3-[4-[4-(3-Methylphenyl)-1-piperazinyl]butyl]hydantoin

To a solution 12.4 g of 1-(4-aminobutyl)-4-(3-methylphenyl)piperazine in 75 ml of toluene is added 7.75 g of ethyl isocyanoacetate. After a mild exothermic reaction has subsided, the solution is heated at 90-100°C for 30 minutes. The resulting solution of N-[[4-[4-(3-methylphenyl)-1-piperazinyl]-butyl]carbamoyl]glycine, ethyl ester is treated with 110 ml of 20% hydrochloric acid and the mixture is stirred and heated at 90-100°C for four hours while the toluene is allowed to evaporate. The remaining mixture is evaporated under reduced pressure, and the residue is dissolved in 200 ml of ethanol-benzene (1:1). The solution is evaporated to dryness under reduced pressure. The residue is dissolved in 100 ml of isopropanol, and the result solution is concentrated by distillation to a volume of approximately

50 ml in order to remove all of the excess water and hydrochloric acid. Ether (150 ml) is added to the concentrate and on cooling 12.7 g of product melting at 166-170°C is obtained. Two recrystallizations from isopropanol yields 9.4 g of analytically pure product as the hydrochloride salt; mp 184-6°C.

EXAMPLE 2

3-[4-[4-(4-Methylphenyl)-1-piperazinyl]butyl]hydantoin

By following the general procedure described in Example 1 10.8 g of 3-[4-[4-(4-methylphenyl)-1-piperazinyl]butyl]hydantoin monohydrochloride melting at 231-5°C is obtained from 12.5 g of 1-(4-aminobutyl)-4-(4-methylphenyl)piperazine treated with 7.75 g of ethyl cyanatoacetate in toluene.

EXAMPLE 3

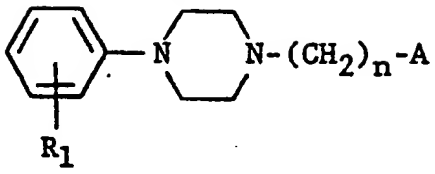
5,5-Dimethyl-3-[[4-(3-ethoxyphenyl)-1-piperazinyl]-butyl]amino]-2-cyclohexen-1-one

A solution of 13.9 g of 1-(4-aminobutyl)-4-(3-ethoxyphenyl)piperazine and 7.0 g of 5,5-dimethyl-1,3-cyclohexanedione in 80 ml of toluene is heated at reflux with a water separator for four hours, or until one equivalent of water is separated. The solution is treated with charcoal and filtered. Pentane is added to the warm solution until cloudy and on standing 18.1 g of product, mp 115-117°C is obtained.

Calcd for $C_{24}H_{37}N_3O_2$ (399.6): C, 72.13%; H, 9.33%; N, 10.52%

Found: C, 72.10%; H, 9.31%; N, 10.42%.

The following compounds were prepared by procedures similar to those described in the examples.

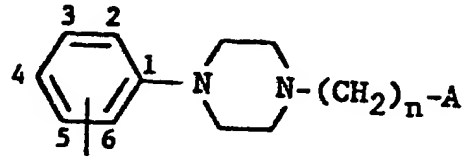


| | $R_1$ | n | A | mp | Procedure of Example |
|---|---|---|---|---|---|
| 1 | H | 3 | $A_1$** | 265-268°C dec | 1 |
| | 2-$CH_3$ | 4 | $A_1$* | 232-234°C | 1 |
| | 3-$CH_3$ | 3 | $A_1$* | 233-236°C dec | 1 |
| | 3-$CH_3$ | 4 | $A_1$* | 184-187°C | 1 |
| 5 | 4-$CH_3$ | 4 | $A_1$* | 231-235°C | 1 |
| | 2-$OCH_3$ | 2 | $A_1$* | 240-243°C | 1 |
| | 2-$OCH_3$ | 3 | $A_1$** | 235-238°C | 1 |
| | 2-$OCH_3$ | 4 | $A_1$* | 227-229.5°C | 1 |
| | 3-$OC_2H_5$ | 4 | $A_1$* | 157.5-159°C | 1 |
| 10 | 4-$OCH_3$ | 3 | $A_1$* | 234-236°C | 1 |
| | 2-O$\underline{i}C_3H_7$ | 4 | $A_1$* | 209-215°C | 1 |
| | | | | | |
| | H | 3 | $A_2$ | 159-160°C | 3 |
| | 2-$CH_3$ | 4 | $A_2$ | 98-99°C | 3 |
| | 3-$CH_3$ | 3 | $A_2$ | 140-140.5°C | 3 |
| 15 | 3-$CH_3$ | 4 | $A_2$ | 141.5-144°C | 3 |
| | 4-$CH_3$ | 3 | $A_2$ | 182-183°C | 3 |
| | 2-$OCH_3$ | 4 | $A_2$ | 115-117°C | 3 |
| | 3-$OCH_3$ | 3 | $A_2$ | 147-148°C | 3 |
| | 3-$OC_2H_5$ | 4 | $A_2$ | 115-117°C | 3 |

20 *hydrochloride salt
**dihydrochloride salt

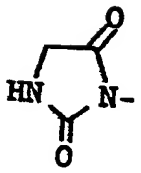
CLAIMS for the designated States BE, CH, DE, FR, GB, IT, LI, LU, NL and SE:

1. A compound having the structural formula:



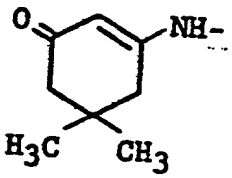
I

wherein A is



$A_1$

or



$A_2$

n is 2, 3 or 4; and $R_1$ is a hydrogen atom, an alkyl radical having from one to six carbon atoms or an alkoxy radical having from one to six carbon atoms; or a pharmaceutically acceptable salt thereof; with the provisos that: when A is $A_1$ and n is 3, $R_1$ is not 3-$OCH_3$; when A is $A_2$ and n is 3, $R_1$ is not 2-$OCH_3$ or 4-$OCH_3$; and, when A is $A_2$ and n is 4, $R_1$ is not 4-$CH_3$ or 4-$OCH_3$.

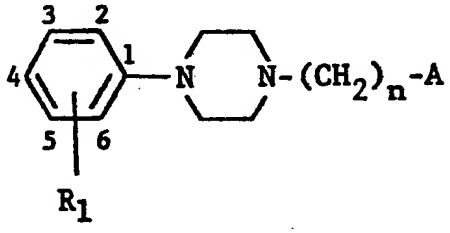
2. A compound as claimed in Claim 1, having the name 3-[4-[4-(3-methylphenyl)-1-piperazinyl] butyl]-hydantoin, or a pharmaceutically acceptable

salt thereof.

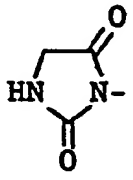
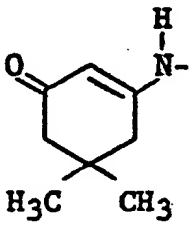
3. A compound as claimed in Claim 1, having the name 3-[4-[4-(4-methylphenyl)-1-piperazinyl]butyl]-hydantoin, or a pharmaceutically acceptable salt thereof.

4. A compound as claimed in Claim 1, having the name 5,5-dimethyl-[3-[[4-(3-ethoxyphenyl)-1-piperazinyl]butyl]amino]-cyclohex-2-en-1-one, or a pharmaceutically acceptable salt thereof.

5. A process for producing a compound having the structural formula I



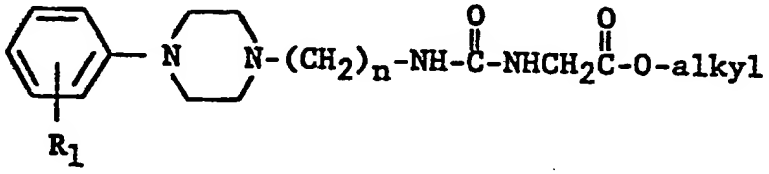
or a pharmaceutically acceptable salt thereof

wherein A is  or  ,

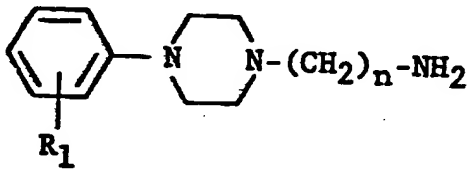
$A_1$ $A_2$

n is 2, 3 or 4; $R_1$ is a hydrogen atom, an alkyl radical having from one to six carbon atoms or an alkoxy radical having from one to six carbon atoms; with the provisos that: when A is $A_1$ and n is 3, $R_1$ is not 3-$OCH_3$; when A is $A_2$ and n is 3, $R_1$ is not 2-$OCH_3$

or 4-$OCH_3$; and, when A is $A_2$ and n is 4, $R_1$ is not 4-$CH_3$ or 4-$OCH_3$; which process comprises the steps of cyclizing a compound of the following structural formula II



wherein $R_1$ and n are as defined above, or a salt thereof, by reaction with a strongly acidic or basic cyclizing agent to form a compound of structural formula I where A is $A_1$; or reacting a compound of the following structural formula III

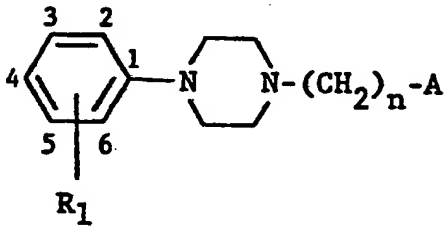


wherein $R_1$ and n are as defined above, with 5,5-dimethyl-1,3-cyclohexanedione to form a compound of structural formula I where A is $A_2$; thereafter isolating the compound of structural formula $IA_1$, or $IA_2$; and, if desired, converting the isolated compound to a pharmaceutically acceptable salt.

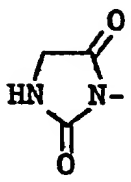
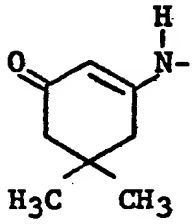
6. A pharmaceutical composition comprising a compound as claimed in Claim 1 in combination with a pharmaceutically acceptable carrier.

CLAIMS for the State AT:

1. A process for producing a compound having the structural formula I



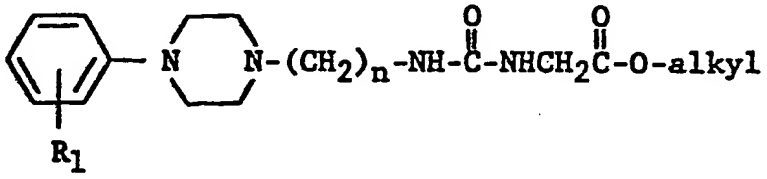
or a pharmaceutically acceptable salt thereof

wherein A is  or  ,

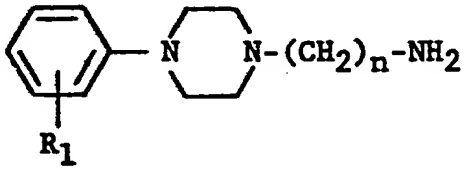
$A_1$ $A_2$

n is 2, 3 or 4; $R_1$ is a hydrogen atom, an alkyl radical having from one to six carbon atoms or an alkoxy radical having from one to six carbon atoms; with the provisos that: when A is $A_1$ and n is 3, $R_1$ is not 3-$OCH_3$; when A is $A_2$ and n is 3, $R_1$ is not 2-$OCH_3$

or 4-$OCH_3$; and, when A is $A_2$ and n is 4, $R_1$ is not 4-$CH_3$ or 4-$OCH_3$; which process comprises the steps of cyclizing a compound of the following structural formula II



wherein $R_1$ and n are as defined above, or a salt thereof, by reaction with a strongly acidic or basic cyclizing agent to form a compound of structural formula I where A is $A_1$; or reacting a compound of the following structural formula III



wherein $R_1$ and n are as defined above, with 5,5-dimethyl-1,3-cyclohexanedione to form a compound of structural formula I where A is $A_2$; thereafter isolating the compound of structural formula $IA_1$, or $IA_2$; and, if desired, converting the isolated compound to a pharmaceutically acceptable salt.

2. A process according to Claim 1, for producing 3-[4-[4-(3-methylphenyl)-1-piperazinyl] butyl]-hydantoin, or a pharmaceutically acceptable salt thereof.

3. A process according to Claim 1, for producing 3-[4-[4-(4-methylphenyl)-1-

piperazinyl]butyl]-hydantoin, and the pharmaceutically acceptable salts thereof.

4. A process according to Claim 1, for producing 5,5-dimethyl-[3-[[4-(3-ethoxyphenyl)-1-piperazinyl]butyl]amino]-cyclohex-2-en-1-one, or a pharmaceutically acceptable salt thereof.

5. A process for producing a pharmaceutical composition, which comprises combining a compound of formula I as defined in Claim 1 or a pharmaceutically acceptable salt thereof, with a pharmaceutically acceptable carrier.